Office Action Summary	Application No.	Applicant(s)	
	10/759,315	BLECK ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12,14-18,20-26,28 and 30-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 12, 14-18, 20-26, 28, and 30-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/01/2008 has been entered.

Claims 11, 13, 19, 27, 29, and 42 have been cancelled. Claims 1, 26, and 28 have been amended.

Claims 1-10, 12, 14-18, 20-26, 28, and 30-41 are pending and under examination.

Withdrawn Rejections

2. The following nonstatutory obviousness-type double patenting rejections are withdrawn because Applicant submitted terminal disclaimers on 05/28/2008:

The rejection of claims 1-10, 18, 20-26, 28, 30-34, 39, and 41 as being obvious variants of claims 18-20, 22, 28-37, 42-46 of copending Application No. 10/397079.

The rejection of claims 1-10, 12, 14-18, 20-26, 28, 30-34, and 39-41 as being obvious variants of claims 9-12 and 14-22 of U.S. Patent No. 6,852,510.

The rejection of claims 1-10, 12, 14-18, 20-26, 28, 30-34, and 39-41 as being obvious variants of claims 110-124 of Application No. 11/018,895, now Patent No.

7,332,333.

Upon further consideration, the following rejections are withdrawn in favor of new rejections using supplementary secondary references which provide additional evidence that one of skill in the art would have known and would have been motivated to arrive at the claimed invention:

The rejection of claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. (Proc. Natl. Acad. Sci. USA,1996, 93: 10371-10376), in view of both Felts et al. (Strategies,1999, 12: 74-77) and Inaba et al. (J. Surg. Res., 1998, 78: 31-36).

The rejection of claims 1-10, 12, 14-18, 20, 21, 26, 28, 30-34, and 41under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with Felts et al. and Inaba et al., in further view of Burns et al. (Proc. Natl. Acad. Sci. USA, 1993, 90: 8033-8037).

The rejection of claims 1-10, 12, 14, 18, 20, 21, 26, 28, 30-38, and 41 under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with Felts et al. and Inaba et al., in further view of Schroder et al. (Biotech. Bioeng., 1997, 53: 547-559).

The rejection of claims 1-10, 12, 14, 18, 20-24, 26, 28, 30-34, and 39-41 under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with Felts et al. and Inaba et al., in further view of both Primus et al. (Cancer Res., 1997, 53: 3355-3361) and Kolb et al. (Hybridoma, 1997, 16: 421-426, Abstract).

The rejection of claims 1-10, 12, 14, 18, 20, 21, 25, 28, 30-34, and 41 are under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with Felts et al. and Inaba et al., in further view of Naldini et al. (Science, 1996, 272: 263-267).

New Rejections

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-10, 12, 14-18, 20-26, 28, and 30-41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 36-74 and 94-102 of copending Application No. 11/928,464, in view of Schroder et al. (Biotech. Bioeng., 1997, 53: 547-559, of record).

This is a provisional obviousness-type double patenting rejection.

The instant claims are drawn to a method for transducing host cells by providing an immortal host cell and a plurality of retroviral vectors encoding a gene of interest, contacting the host cell at a multiplicity of infection from about 10 to 1000, repeating the

above steps a plurality of time, clonally selecting the host cell expressing the gene of interest, and purifying the protein of interest (claims 1-10, 25, 28, 30, and 31). The retroviral vector is pseudotyped and comprises MoMLV elements, an exogenous promoter, a signal sequence, and an amplifiable marker such as DHFR (claims 12, 14-18, 20, 35, and 36) and the vector encodes at least two proteins, such as immunoglobulin heavy and light chains, arranged in a polycistronic sequence (i.e., the retroviral vector comprises IRES) (claims 22-24 and 39). Clonally selected cells are cultured in the presence of a selection agent such as mehtotrexate and could express 1, 10, or 50 pg per cell per day of the protein of interest (claims 32-34, 37, and 38), and the host cell comprises from 20 to about 100 integrated retroviral vectors (claim 41). The host cell can be a CHO or a 293 cell (claim 26) and the host cell can be transduced with at least two different vectors encoding different genes of interest (claim 40).

The application claims recite a method of transfecting a host cell and producing a protein of interest by providing a host cell and retroviral vectors comprising an exogenous promoter, a gene encoding for a protein of interest, contacting the host cell with the retroviral vector at a multiplicity of infection of 1000, and culturing the transduced host cell such that the protein encoded by the gene of interest is produced, wherein between 2 and 1000 copies of retroviral vector integrate into the host cell genome; the host cell could be clonally selected and the protein of interest is further isolated (claims 36-43, 49, 51, 54, 56, 58-67, 69, 71-74, and 94-101). The retroviral vector is pseudotyped and comprises MoMLV elements, a signal sequence, an RNA stabilizing element IRES, at least two gene of interest such as the immunoglobulin

genes arranged in a polycistronic sequence, the host cell is a CHO cell (i.e., immortal cell), the host cell secretes 1, 10, or 50 pg per cell per day of the protein of interest, and the host cell could comprise a second retroviral vector encoding a second protein of interest (claims 36-38, claims 44-48, 50, 52, 53, 55, 57, 68, 70, and 102). The application claims do not recite DHFR and methotrexate. Schroder et al. teach the amplification of hATIII expression in CHO cells via DHFR-mediated gene amplification in the presence of methotrexate (Abstract, Introduction, Table I). It would have been obvious to one of skill in the art, at the time the invention was made, to include an amplifiable marker, such as DHFR, into the instant vector and select with methotrexate for increased protein production, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Schroder et al. teach that increase synthesis of recombinant proteins in animal cells is commonly achieved by using gene amplification. One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such a composition can be successfully made and used.

Thus, at the time of the invention, one of skill in the art would have considered the instantly pending claims an obvious variation of the application claims when viewed in light of the teachings of Schroder et al.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. (Proc. Natl. Acad. Sci. USA,1996, 93: 10371-10376, of record), in view of each Felts et al. (Strategies,1999, 12: 74-77, of record), Wang et al. (Gene Therapy, 2000, 7: 196-200), Zhou et al. (Mol Endocrinol, 1989, 3: 1157-1164, Abstract), and Inaba et al. (J. Surg. Res., 1998, 78: 31-36, of record).

Mathor et al. teach a retroviral vector encoding human interleukin 6 (hIL-6), wherein the retroviral vector contains MoMLV LTRs, wherein the vector is used to transduce keratinocytes at a MOI of 30, wherein the keratinocytes integrate multiple proviral copies in their genome, and wherein the transduced keratinocytes secrete hIL-6 at a rate of approximately 800 ng per 10^6 cells per day during their lifetime (i.e., the cells secrete more than 1 pg per cell per day); the transduced cells are grown as mass cultures or are cloned by limiting dilution (claims 1, 18, 20, 28, 31, 32) (Abstract, p. 10371, column 2, second paragraph, Material and Methods, p. 10372, columns 1 and 2, p. 10373, column 2). Since hIL-6 is secreted, the retroviral vector must necessarily comprise a segment encoding a secretion signal sequence operably linked to the gene encoding for hIL-6 (claim 21). Mathor et al. teach clonal analysis by Southern blot and by radioimmunoassay, wherein the radioimmunoassay is performed on isolated hIL-6 (claims 1, 30) (p. 10372, columns 1 and 2, p. 10374, p. 13075, column 1 and Fig.4, p. 10636, column 1). Mathor et al. teach 11 clones with 1 to 15 proviral integrations, i.e.,

Mathor et al. teach clonally selecting at least 1 or 10 colonies (claims 35 and 36) (p. 10373, Table 1). Mathor et al. also teach that the retroviral vector is produced from packaging cell lines transfected with an envelope plasmid and a vector plasmid, wherein the packaging cell line expresses gag and pol proteins (claims 12 and 14) (p. 10371, column 2 bridging p. 10372).

Mathor et al. teach using secondary cell cultures and not immortal cells (claim 1). However, at the time the invention was made, the prior art taught the use of immortal cells as host cells for retroviral vectors. For example, Zhou et al. teach efficient expression of transgene in immortal cells such as 208F cells by transducing these cells with a retroviral vector expressing the transgenes (Abstract). Therefore, one of skill in the art would have known that immortal cells could also be used in the method of Mathor et al. and would be motivated to modify the method of Mathor et al. by substituting their secondary cells with immortal cells to achieve the predictable result of obtaining consistent production of desired proteins for unlimited time.

Mathor et al. and Zhou et al. do not specifically teach a genome comprising from 20 to about 100 integrated vectors (claims 1 and 41). However, Mathor et al. do teach that protein expression is directly proportional to the integration events (i.e., copy number) (p. 10376, column 1). Additionally, the prior art as a whole teaches that there is a positive correlation between the MOI, integration events, and transduction efficiency. For example, Felts et al. teach that the advantage of retroviral vectors is that the copy number of integrated provirus can easily be controlled by varying the multiplicity of infection (MOI) (p. 74). Wang et al. teach transducing keratinocytes *in*

vitro with a retroviral vector at MOI of 100-1000, wherein a MOI of 1000 results in maximum gene transfer with no detrimental effects on cell morphology and growth (Abstract, p. 197, column 2, first full paragraph, p. 198, Fig. 2 and 3, p. 199, column 2, second full paragraph). Based on these teachings, one of skill in the art would have known that high MOI are not detrimental to keratinocytes and that increasing MOI would result in increased proviral integration events. It would have been obvious to one of skill in the art, at the time the invention was made, to use different MOIs to achieve the claimed ranges of integration events, with a reasonable expectation of success. The motivation to do so is provided by Mathor et al., who teach the possibility of specifying the level of transgene expression by controlling the integration events (Abstract, p. 10376, column 1). One of ordinary skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that the level of retroviral vector integration events can be easily controlled by manipulating the MOI. With respect to the limitations of one cell secreting more than 10 or 50 pg protein per day (claims 33 and 34), one of skill in the art would have had known to obtain the desired amounts of synthesized proteins by controlling the number of integration events.

Mathor et al., Zhou et al., and Wang et al. do not teach serially transducing the cells (claims 2-10). Inaba et al. teach a method of transducing cells by contacting the cells with viral supernatant 4-6 times over a 10-14 day period, wherein serially transducing the cells results in increased transduction efficiency (p. 32, column 2, first paragraph, Fig.1, p. 34, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al. by using serial

transduction, with a reasonable expectation of success. The motivation to do so is provided by Inaba et al., who teach that serial transduction results in higher transduction rates. Given these teachings, one of skill in the art would have found it obvious to repeat the infection protocol as many times as necessary to achieve the desired level of protein production. One of skill in the art would have been expected to have a reasonable expectation of success in using such a method because the art teaches that serial transduction can be successfully used to increase transduction efficiency.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments are answered below to the extent that they pertain to the instant rejection.

Applicant argues that Mathor, Felts and Inaba are directed to gene therapy uses and infection of primary cell cultures. The references do not teach or suggest the use of immortalized cells as presently claimed. Applicant next submits that, in the April 24 interview, the Examiners argued that Applicant was relying on gene therapy references to establish the state of the art, and that those references did not apply to the of immortalized cell lines for the production of recombinant proteins. Although Applicant disagrees for the reasons outlined below, Applicant notes that if the gene therapy references cited by Applicant are not applicable for establishing the state of the art for using immortalized cell lines for recombinant protein production, then gene therapy references are not properly applicable for rejecting the current claims which are limited

to the use of immortalized cell lines, i.e., those references are non- analogous art. For the reasons cited in the Second Bleck Declaration (Bleck Decl. 2), Applicant submits that a person of skill in the art would not have introduced greater than 20 retroviral vectors into an immortalized cell line to produce recombinant protein because the accepted wisdom was that this process would result in a decrease in protein production due to viral interference, gene silencing or methylation. Thus, Applicant proceeded contrary to the established state of the art in seeking to make cell lines in which the cells contain more than 20 integrated retroviral vectors (MPEP 2145(X)(D)(3)). In Dr. Bleck's previous Declaration (Bleck Decl. 1), he stated that references such as Arai et al. (Virology, 1999, 260:109-115) and Coffin et al. (Development and Applications of Retroviral Vectors, Chapter 9 in Retroviruses, 1997, p. 437-473), specifically teach away from the current claims and that one of skill in the art would be "discouraged" from using a the claimed multiplicity of infection and copy insert number to obtain cells for the production of a secreted protein. Applicant points out that the Examiner has attempted to rebut the evidence in Bleck Decl. 1 primarily by relying on the Kustikova and Zielske references in pages 8 and 9 of the Office Action. At page 13 of the Office Action, the Examiner indicates that Kustikova and Zielske are "prior art made of record." Applicant contests the characterization of these references as prior art. In the interview, the Examiner's acknowledged that the references were not prior art. This issue is addressed in Paragraph 6 of the Bleck Declaration. In fact, both references were published well after either the filing date of the parent application (filed June 29, 2001), which contains support the serial transduction limitations and

integration ranges claimed in this application, or the instant application, filed January 16, 2004. As stated by Dr. Bleck, Kustikova and Zielske were published well after the disclosure in the parent patent application. Contrary to the Examiner's assertions, these references confirm to a person of skill the art the uncertainty that was associated with introducing multiple copies of a retroviral vector into a host cell. With respect to Arai et al., Dr. Bleck in Bleck Decl. 2 states:

> "the Examiner makes several assumptions here that are either scientifically incorrect or that have a better scientific explanation. First, the Examiner assumes that the cells that do not die have a very high copy number of integrated vectors. There is no evidence for this. Arai did not clone or determine the number of integrated vectors in those cells. Second, a person of ordinary skill in the art would expect that the surviving cells did not have high numbers of integrations. Retroviral vectors do not transduce cells that are not dividing. The most reasonable explanation is that the surviving cells were not undergoing cells division during the transduction period and thus did not become transduced or that the cells were at point in the cells cycle so that they were not exposed to vector at the optimum time period for transduction and thus only had low numbers of integrations. A person of skill in the art would believe that this is a valid explanation, especially when Arai teaches that the major factor for apoptosis was probably a high number of integrations and insertional mutagenesis."

With respect to Coffin et al., Dr. Bleck addresses this issue in Paragraph 5 of Bleck Decl. 2:

> "Coffin et al. confirms the teaching of Arai et al. that the incorrect use of retroviral vectors can lead to insertional mutagenesis. Furthermore, the Examiner's assumption that malignant transformation or other mutagenesis would not impede an immortalized mammalian cell from producing a protein of interest has no scientific basis. In fact, if an immortalized mammalian cell is mutagenized or transformed in some way by the vector, it is almost certain that production of the desired protein would be affected. The recombinant protein production industry relies on the use of standardized immortalized mammalian cells whose growth is predictable. Cells with additional mutations would be highly undesirable."

Dr. Bleck further presents additional evidence in Bleck Decl. 2 that establishes that the present invention proceeded contrary to the accepted wisdom in the art. First, a

person of skill in the art reading Kustikova would be discouraged from attempting to use the claimed methods because "Kustikova actually shows is that those of skill in the art would have been discouraged from intentionally making cell lines with high numbers of retroviral integration because of insertional mutagenesis." Bleck Decl. 2, Para. 7. Likewise, Zielske found that transgene expression reach a plateau after four integrations. To a person of skill in the art, "this further teaches away from the claimed methods - if only four integrations are needed for maximum expression, why introduce more? As shown in the next paragraphs, those of skill in the art believed that expression reached a plateau because of viral interference, gene silencing or methylation." Bleck Decl. 2, Para. 8. Dr. Bleck also provides two additional references that demonstrate that the inventors proceeded contrary to the accepted wisdom in the art, such as Walker et al. (Human Gene Therapy, 1996, Vol. 7, No. 9:1131-1138 (Tab 1)), who teach that: "Simultaneous retroviral transductions were infrequent events. In addition, transduction of previously infected cells (sequential transductions) occurred at lower than expected frequencies. Our data suggest that there is quantifiable viral interference in sequential retroviral transductions. This interference occurs by a mechanism that appears to be independent of the amphotropic retroviral receptor." Likewise, Bestor (J. Clin. Invest., 2000, 105(4):409-411) teaches retroviruses and repeated genes are often silenced or suppressed by mammalian cells. According to Dr. Bleck, "because of viral interference and gene silencing or suppression, a person of ordinary skill in the art would be discouraged from using sequential transductions to increase viral inert number and would be discouraged from attempting to create immortalized mammalian cell lines with

the claimed number of insertions." In the Interview on April 24, 2008, the Examiner and the Examiner's supervisor indicated that the teachings Kustikova, Zielske, Walker and Bestor were related to gene therapy and thus not applicable to immortalized mammalian cell cultures. Dr. Bleck disagrees with this because the prior art concern with viral interference, gene suppression and gene silencing would apply regardless of the situation was gene therapy or making immortalized mammalian cells to produce a protein of interest: "if it is the Examiner's position that those references only apply to gene therapy situations, then gene therapy prior art references such as Mathor et al., which addresses the use of normal human keratinocytes for gene therapy, Felts et al., which addresses "fields for which highly efficient gene delivery is essential" and refers specifically to gene therapy, and Inaba et al., which addresses the use of endothelial cells for gene therapy (as well as Kustikova and Zielske), do not apply to the use of retroviral vectors in immortalized mammalian cells such as those exemplified throughout the patent application." Applicants further note that the Examiner's assertions with respect to Mathor et al. are misplaced. In particular, in the Interview the Examiners indicated that this Table shows that increasing the number of integrations increases protein production. According to Dr. Bleck, "a person of ordinary skill in the art would not interpret the data in that manner. The data shows that at 8 integrations, 1140 ng/106 cells/day of protein is produced, and that when 15 integrations were obtained, the protein production decreased to 1014 ng/106 cells/day or protein produced. This indicates that protein production had reached a plateau and that further introduction of retroviral vectors did no good or decreased protein production. Thus, one of skill in the

art would conclude from the data that additional integrations past 8 integrations were not needed or not desirable." This evidence is also directly applicable to the Examiner's assertion that "the art teaches the number of integrations per cell as being a result-effecting variable and therefore, one of skill in the art would be motivated to use a range of integrations (obtained by varying MOIs) to obtain optimum results." The evidence presented above establishes that, contrary to the Examiner's assertions, a person of skill in the art would be discouraged by the state of the art from introducing from 20 to 100 retroviral vectors into an immortalized cell.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

The argument that Mathor et al. do not teach using immortal cells as *in vitro* host is not found persuasive because using such cells as hosts would have been obvious to one of skill in the art (see above). Applicant argues that Mathor et al. and Inaba et al. are not pertinent to the claimed invention because they are directed to gene therapy, and therefore, they are not analogous art. In response to this argument, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Mathor et al. and Inaba et al. clearly teach a method of *in vitro* obtaining host cells comprising multiple retroviral copies in their genome for increased production of proteins of interest, which is exactly what Applicant claims; such is not gene therapy.

One of skill in the art would have easily recognized that their teachings pertain to protein production *in vitro*. The fact that they further suggest transplanting such host cell in animals does not disqualify the references as prior art; the fact of the matter is that Mathor et al. and Inaba et al. do teach increased protein production *in vitro* by integrating multiple retroviral copies into the genome of a host cell. Therefore, both Mathor et al. and Inaba et al. are pertinent to the particular problem with which the applicant was concerned. With respect to Felts et al., the reference is directed to cloning and not gene therapy. With respect to Kustikova et al. and Zielske et al., Applicant is right in pointing out that they do not qualify as prior art; identifying such references as prior art was an inadvertent error due to the fact that the Examiner used an OACS formed paragraph and omitted to delete the word “prior”. However, these post-filing references were cited to demonstrate that, contrary to Applicant's assertions, one of skill in the art would not have been discouraged by the teachings of Arai et al. and Coffin et al. to obtain higher integration events by increasing the MOI (see the final Office action of 01/09/2008). Importantly, even the prior art teaches using MOI as high as 1000 for efficient and stable transduction, without detrimental effects to the cells (see Wang et al. above). All references above demonstrate that the art does not discourage to use high MOI to transduce cells *in vitro*. With respect to Arai, Applicant argues that the Examiner has no evidence for the assertion that the surviving 3Y1 cells do not die and comprise high proviral copy numbers in their genome. While this is true, it is noted that besides arguing that the Examiner has no scientific basis for such an assertion, Applicant provides no evidence for the explanation that all remaining 3Y1 cells survive

because they do not undergo mitosis, and therefore, are not transduced. As Applicant points out, Arai did not clone or determine the number of integrated vectors in the surviving cells, and therefore, Applicant explanation is not supported by any evidence. An explanation does not equal evidence. Moreover, Arai's teaching of an MOI of 100 as causing cell death specifically refers to the 3Y1 cells; they also use NIH3T3 cells, which do not die when using a pseudotyped retrovirus at an MOI of 100 (see p. 112, column 1, first full paragraph and Fig. 3). Therefore, NIN3T3 cells are viable at MOI of 100; keratinocytes are also viable and retain their phenotype as MOI of 1000 (see Wang et al. above). Therefore, based on the teachings of the art as a whole, one of skill in the art would know that high MOI could be used to obtain cells with high numbers of proviral copies in their genome. With respect to Coffin, it is noted that the reference was not used in the instant rejection. However, in response to Applicant's argument, it is noted that the reference refers to the *in vivo* use of retroviral vectors in animals and humans. Applicant's assertion of safety concern is not an issue in the instant case, because the claims encompass a host cell *in vitro* and the combined teachings of Mathor et al. and Felts et al. are drawn to the *in vitro* production of recombinant proteins. Coffin et al. refer to gene therapy in humans where malignant transformation can endanger the patient life, which cannot be compared to a cell in culture, wherein malignant transformation does not endanger anybody's life and does not impede the cell from producing the protein of interest and from being cloned (see also below). Therefore, Coffin et al. do not teach away from the instant invention. Applicant argues that malignant transformation of cells *in vitro* is almost certain to affect the production of the

desired protein. Again, this is an assertion not supported by evidence. Applicant argues that Kustikova et al. show that one of skill in the art would have been discouraged from intentionally making cell lines with high retroviral integration because of insertional mutagenesis. Such an argument is not found persuasive because Kustikova et al. teach limiting integration for gene therapy and not cells in culture. In fact, Kustikova et al. teach a linear correlation between MOI and integration events and increased protein expression levels from MLV vectors with increased integration, providing evidence that insertional mutagenesis does not interfere with protein production *in vitro*, as Applicant argues (Abstract, p. 3934, column 1, p. 3936, column 1 and Fig. 1B, p. 3937, column 2). With respect to Zielske et al. they teach that, regardless of the copy number, there is a practical limit in the degree of gene expression which can be achieved with their retroviral vector in the particular cell they use due to the presence of the CMV promoter in their vector as opposed to the MLV vector of Kustikova et al., which does not have the CMV promoter and thus can attain increasing levels of transgene expression with increased copy numbers (p. 926, column 2, p. 929, column 1, third paragraph). Therefore, since the rejection is based on references teaching a vector which does not have the CMV promoter, this argument is not found persuasive. Applicant also submits new references (i.e., Walker et al. and Bestor et al.) as proof that the art teaches away from the instant invention. With respect to Walker et al., it is noted that the reference is related to transducing a single cell with two distinct retroviral vectors (i.e., vectors based on murine Maloney sarcoma virus and Harvey virus) and demonstrate that simultaneous retroviral transduction (i.e., with two

distinct vectors) was infrequent; Walker et al. conclude that transduction of the cell with one viral vector type interferes with the cell being transduced by another vector type, i.e., their teachings are applicable when transducing the same cells with two distinct vector types (Abstract, Overview Summary, p. 1137, column 1). Such teaching is irrelevant for the claimed invention, which is drawn to transduction with a single retroviral vector type, and therefore, interference from another vector type is not a problem. With respect to Bestor, the reference is related to silencing *in vivo* and not cells *in vitro*. For example, Bestor teaches that, while fibroblasts transduced with retroviral vectors stably expressed adenosine deaminase *in vitro*, transplantation of these cells into mice resulted in decreased adenosine deaminase expression (p. 409, column 2, last paragraph). With respect to Mathor et al., Applicant argues that they indicate that protein production reaches a plateau and that introduction of more than 8 copies (i.e., 15) did not result in increased protein expression. In response to this argument, it is noted that Table 1 (to which Applicant refers) shows the result obtained with only one keratinocyte clone for each 8 and 15 integration events. Such results cannot be extrapolated to all clones. The art teaches that retroviral insertion is random and that expression level is dependent on the insertion sites (see Mathor et al., p. 10376, column 1; Liu et al., Anal Biochem, 2000, 280: 20-28, Abstract, p. 21, column 1; Stamps et al., Int J Cancer, 1994, 57: 865-874, Abstract, p. 868, column 1, p. 869, Fig. 2). Based on these teachings, one of skill in the art would expect clones with the same number of copies to have different expression levels, and therefore, would know to select multiple clones and look for the high expressing ones. For these reasons, both

Applicant's arguments and 132 declaration are not found persuasive and the rejection is maintained.

7. Claims 1-10, 12, 14-18, 20, 21, 26, 28, 30-34, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with each Felts et al., Wang et al., Zhou et al., and Inaba et al., in further view of Burns et al. (Proc. Natl. Acad. Sci. USA, 1993, 90: 8033-803, of record).

The teachings of Mathor et al., Felts et al., Wang et al., Zhou et al., and Inaba et al. are applied as above for claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41. Mathor et al., Felts et al., Wang et al., Zhou et al., and Inaba et al. do not teach 293-GP cells (claim 15), VSV-G protein (claims 16 and 17), or baby hamster kidney (BHK) cells (claim 26). Burns et al. teach producing retroviral vectors pseudotyped with VSV-G, wherein the vectors are produced in 293-G cells and wherein the pseudotyped retroviral vectors are able to mediate stable gene transfer in cells that cannot be infected by the wild type retroviral vectors, such as BHK cells (claim 26) (Abstract, p. 8033, columns 1 and 2, p. 8035, column 1, second paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al. Felts et al., Wang et al., Zhou et al., and Inaba et al. by using the pseudotyped retrovirus of Burns et al., with a reasonable expectation of success. The motivation to do so is provided by Burns et al., who teach that such a virus has an expanded host range. One of skill in the art would have been expected to have a reasonable

expectation of success in making and using such a composition because the art teaches that such a composition can be successfully made and used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Burns et al. do not cure the deficiencies noted above. Applicant's argument is acknowledged, however, the rejection is maintained for the reasons above.

8. Claims 1-10, 12, 14, 18, 20, 21, 26, 28, 30-38, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with each Felts et al., Wang et al., Zhou et al., and Inaba et al., in further view of Schroder et al. (Biotech. Bioeng., 1997, 53: 547-559, of record).

The teachings of Mathor et al., Felts et al., Wang et al., Zhou et al., and Inaba et al. are applied as above for claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41. Mathor et al., Felts et al., Wang et al., Zhou et al., and Inaba et al. do not teach DHFR and culturing the transduced cells in the presence of methotrexate (claims 35-38), nor do they teach Chinese hamster ovary (CHO) cells (claim 26). Schroder et al. teach the amplification of hATIII expression in CHO cells via DHFR-mediated gene amplification in the presence of methotrexate (Abstract, Introduction, Table I). It would have been obvious to one of skill in the art, at the time the invention was made, to include an amplifiable marker, such as DHFR, into the vector of Mathor et al., Felts et al., Wang et al., Zhou et al., and Inaba et al. for increase protein production and to use the modified

vector for the transduction of CHO cells, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Schroder et al. teach that increase synthesis of recombinant proteins in animal cells is commonly achieved by using gene amplification. One of skill in the art would have been motivated to use CHO cells because they are known to be an excellent model cell line for the production of high levels of proteins of interest. One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such a composition can be successfully made and used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Schroder et al. do not cure the deficiencies noted above. Applicant's argument is acknowledged, however, the rejection is maintained for the reasons above.

9. Claims 1-10, 12, 14, 18, 20-24, 26, 28, 30-34, and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with each Felts et al., Wang et al., Zhou et al., and Inaba et al., in further view of both Primus et al. (Cancer Res., 1997, 53: 3355-3361, of record) and Kolb et al. (Hybridoma, 1997, 16: 421-426, Abstract, of record).

The teachings of Mathor et al., Felts et al., Wang et al., Zhou et al., and Inaba et al. are applied as above for claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41. Mathor

et al., Felts et al., Wang et al., Zhou et al., and Inaba et al. do not teach at least two different vectors encoding different genes of interest (claim 40). Primus et al. teach a method of expressing a monoclonal IgG2a antibody into a tumor cell, wherein the tumor cell is transduced with two different vectors, one encoding the heavy and the other encoding the light chain (claim 40), and wherein the transduced tumor cell produces self-reactive antibodies (Abstract, p. 3355, column 1, p. 3356, column 1, first full paragraph, p. 3360, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Mathor et al., Felts et al., Wang et al., Zhou et al., and Inaba et al. to express antibodies into a cancer cell, as taught by Primus et al., with a reasonable expectation of success. The motivation to do so is provided by Primus et al., who teach that antibody gene transfer into autologous tumor cells offer a new and alternative application in the use of antibodies for the immune therapy of cancer. One of skill in the art would have been expected to have a reasonable expectation of success in making such a composition because the art teaches that such a composition can be successfully obtained.

Mathor et al., Felts et al., Wang et al., Zhou et al., Inaba et al., and Primus et al. do not teach the two genes of interest being arranged in a polycistronic sequence, wherein the genes of interest are the immunoglobulin heavy and light chains (claims 22-24 and 39). Kolb et al. teach concurrent synthesis of both heavy and light chains of the monoclonal antibody A1 by using a bicistronic expression cassette comprising an internal ribosomal entry site (IRES) (Abstract). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al.,

Felts et al., Wang et al., Zhou et al., Inaba et al., and Primus et al. by using the expression cassette of Kolb et al. for the production of monoclonal antibodies of interest, with a reasonable expectation of success. The motivation to do so is provided by Kolb et al., who teach that their method allows for the rapid isolation of cell clones expressing high levels of recombinant antibody. One of skill in the art would have been expected to have a reasonable expectation of success in making such a composition because the art teaches that such a composition can be successfully obtained.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that neither Primus et al. nor Kolb et al. cure the deficiencies noted above. Applicant's argument is acknowledged, however, the rejection is maintained for the reasons above.

10. Claims 1-10, 12, 14, 18, 20, 21, 25, 28, 30-34, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with each Felts et al., Wang et al., Zhou et al., and Inaba et al, in further view of Naldini et al. (Science, 1996, 272: 263-267, of record).

The teachings of Mathor et al., Felts et al., Wang et al., Zhou et al., and Inaba et al. are applied as above for claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41. Mathor et al., Felts et al., Wang et al., Zhou et al., and Inaba et al. do not teach a lentiviral vector (claim 25). Naldini et al. teach lentiviral vector for the stable transduction of non-

dividing cells (Abstract, p. 263, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al., Felts et al., Wang et al., Zhou et al., and Inaba et al. by using the lentiviral vector of Naldini et al., with a reasonable expectation of success. The motivation to do so is provided by Naldini et al., who teach that their vector can be used for the transduction of non-proliferating cells such as hepatocytes, myofibers, hematopietic stem cells, and neurons. One of skill in the art would have been expected to have a reasonable expectation of success in using such a composition because the art teaches that such a composition can be successfully used.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Naldini et al. do not cure the deficiencies noted above. Applicant's argument is acknowledged, however, the rejection is maintained for the reasons above.

Conclusion

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Liu et al. (Anal Biochem, 2000, 280: 20-28) and Stamps et al. (Int J Cancer, 1994, 57: 865-874) were cited in response to Applicant's argument that Mathor et al. teach away from using higher integration events. Specifically, the references teach that retroviral insertion is random, that the integration pattern is

different for different clones, and that expression level is dependent on the insertion sites; therefore, one of skill in the art would expect clones with the same number of copies to have different expression levels, and therefore, would know to select multiple clones and look for the high expressing ones.

12. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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